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Exposure to Ambient Particulate Matter is Associated with Accelerated Functional Decline in Idiopathic Pulmonary Fibrosis

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Abbreviations List:

6MWT = Six minute walk test
AQI = Air Quality Index
ATS = American Thoracic Society
BMI = Body Mass Index
CI = confidence interval
COPD = Chronic Obstructive Pulmonary Disease
EMR = electronic medical record
EPA = Environmental Protection Agency
FVC = Forced vital capacity
GERD = Gastroesophageal reflux disease
GIS = Geographic Information System
ILD = interstitial lung disease
IPF = Idiopathic pulmonary fibrosis
IQR = Interquartile range
NAAQS = National Ambient Air Quality Standard
PFT = Pulmonary function test
PM = Particulate matter
PM10 = Particulate matter with diameter < 10 micrograms in diameter
PM2.5 = Particulate matter with diameter < 2.5 micrograms in diameter
SSDI = Social Security Death Index

Abstract:

Background: Idiopathic pulmonary fibrosis (IPF), a progressive disease with unknown pathogenesis, may in part be due to an abnormal response to injurious stimuli by alveolar epithelial cells. Air pollution and particulate matter inhalation evoke a wide variety of pulmonary and systemic inflammatory diseases. We therefore hypothesized that increased average ambient particulate matter (PM) concentrations would be associated with an accelerated rate of decline in forced vital capacity (FVC) in IPF.

Methods: We identified a cohort of subjects seen at a single university referral center from 2007 to 2013. Average concentrations of particulate matter below 10 and 2.5 micrograms/cubic meter ($\mu\text{g}/\text{m}^3$, PM10 and PM2.5, respectively) were assigned to each patient based on geo-coded residential addresses. A linear multivariable mixed-effects model determined the association between the rate of decline in FVC and average PM concentration, controlling for baseline FVC at first measurement and other covariates.

Results: 135 subjects were included in the final analysis after exclusion of subjects missing repeated spirometry measures and those for whom exposure data were not available. There was a significant association between PM10 levels and the rate of decline in FVC during the study period, with each 5 microgram/cubic meter increase in PM10 corresponding with an additional 46 cc/year decline in FVC ($p=0.008$).

Conclusions: Ambient air pollution, as measured by average PM10 concentration, is associated with an increase in the rate of decline of FVC in IPF, suggesting a potential mechanistic role for air pollution in the progression of disease.

Introduction:

Idiopathic pulmonary fibrosis (IPF) is a progressive fibroproliferative interstitial lung disease (ILD) of uncertain etiology with a median survival of 3 years from diagnosis.¹ IPF is strongly associated with smoking, and case-control studies have demonstrated increased environmental and occupational exposure to a variety of industrial and organic inhalational agents in IPF.²⁻⁵ Cellular and animal models have shown an alteration of the alveolar epithelial cell phenotype in IPF characterized by apoptosis, fibroblast proliferation, and collagen deposition.⁶⁻⁸ These findings suggest a conceptual model of IPF in which genetically susceptible individuals mount an aberrant response to repetitive low-level toxic exposure over time that induces progressive loss of functional alveolar epithelium and macroscopic scarring.⁹

One potential source of repetitive toxic exposure is particulate air pollution. Ambient particles under 10 μ m and 2.5 μ m in diameter (PM10 and PM2.5, respectively) are composed of a complex mixture of organic chemicals, metals, and dusts, largely byproducts of hydrocarbon combustion, that are monitored and regulated by the Environmental Protection Agency (EPA). As the technology to measure daily atmospheric PM levels has improved, PM exposure has been implicated in a diverse range of systemic diseases, from atherosclerosis and diabetes to childhood autism.¹⁰⁻¹³ Ambient PM has been implicated in a wide variety of pulmonary diseases, from decreases in functional pulmonary measures in healthy patients to increased frequency of hospitalizations and mortality in COPD and asthma.^{14,15}

Short-term fluctuations in two other components of air pollution (ozone and nitrogen dioxide) have been associated with increased risk of acute exacerbations of IPF, but the effect of ambient PM on long-term functional measures of disease progression is unknown.¹⁶ We hypothesized that increased exposure to air pollution in the form of ambient PM would be associated with an accelerated rate of decline in pulmonary function in IPF.

Methods:

Patient population

The study population consisted of patients seen at a single university ILD referral center between 2007-2013, who had at least two sets of pulmonary function tests (PFTs) including FVC. We considered the study entry point to be the first recorded FVC in the medical record, and therefore comprised patients seen at follow-up and initial referral visits, and included PFTs that preceded the implementation of the outpatient electronic medical record (EMR) in 2007. We initially identified subjects by EMR query for the standardized diagnostic code for IPF (ICD-9 516.31), and performed manual chart review to confirm that subjects met 2011 American Thoracic Society (ATS) criteria for definite or probable IPF as documented by a subspecialized ILD clinician on the basis of clinical history, radiology, and surgical pathology (when available). In cases of diagnostic uncertainty, a comprehensive review of clinical history, radiology, and surgical pathology were presented to a multidisciplinary committee including at least two ILD clinicians, a dedicated chest radiologist and pathologist for adjudication based on 2011 ATS IPF criteria. The study was approved by the University of Pennsylvania Institutional Review Board (Protocol #817713).

Exposure ascertainment

Exposure to air pollution was characterized using a geospatial approach. The geographic catchment area of the referral center comprised urban, suburban, and rural areas within the greater Philadelphia metropolitan region. Subjects' home addresses were converted into latitude-longitude coordinates (geocoded) using ArcGIS, the industry standard professional geographic information system (GIS) software.¹⁷

Air quality monitoring station location and local daily air quality data were pulled from the Air Quality Index (AQI), an online tool developed by the EPA. Pollution exposure was measured using daily mean concentration levels for PM10 and PM2.5 collected at the air quality monitoring station nearest to the subjects' geocoded address. Local air quality monitoring site locations in the greater Philadelphia region varied during 2007-2013. This resulted in annual AQI data being unavailable for some subjects at certain

times. To overcome these spatial and temporal limitations, all possible site locations were merged across time, enabling an assessment of the closest site reading to each subjects' home address for each exposure variable. Local daily air quality data collected between 2007-2013 were used to generate an individual mean value for each subject for each PM exposure variable from the date of their study entry (January 1, 2007 for subjects that entered prior to this date) through their date of study exit.

In addition, we computed a geospatial measure of automobile-derived air pollution. We used GIS road network data to identify the location and features of every road segment in the study area. Each road was further classified by its primary feature. Using ArcGIS, we calculated the distance between each subjects' geocoded home address and the nearest large road type: highway, state road (connect major cities), and large local roads (intra-state commerce and recreational travel).

Outcomes

The primary outcome was the rate of decline in FVC on serial PFTs, which is a reliable measure of disease status in IPF, a strong independent predictor of mortality, and the standard primary endpoint in clinical trials in IPF.¹⁸⁻²¹ All PFTs available for review from time of initial referral through the end of the study period were included in the analysis. In order to evaluate potential inconsistencies in FVC measurement, we conducted a sensitivity analysis including only tests performed at our university center's pulmonary function laboratory, which were performed by trained personnel according to standardized protocols and met ATS criteria for acceptability and reproducibility.²²⁻²⁵ In order to evaluate the possibility of a survivor effect or measurement error due to exposure preceding the study, we performed an additional sensitivity analysis excluding PFTs performed prior to January 1, 2007. Secondary endpoints included rate of decline in the distance walked during six minute walk testing (6MWT), number of liters of supplemental oxygen required to maintain oxygen saturation > 88% on 6MWT, and all-cause mortality. All 6MWTs performed in our university's pulmonary function lab according to a standardized protocol were included in the analysis.²⁶ Mortality data were abstracted from the EMR, and vital status was additionally assessed using the Social

Security Death Index (SSDI). If there was no documentation of mortality in the medical record or SSDI, all subjects with PFTs within six months of the study endpoint were assumed to be alive.

Statistical analysis

All analyses were conducted in Stata version 12.1. A longitudinal linear mixed-effects model, with random intercept and random slope was chosen based on its assumptions with regard to missing data (missing at random), and to account for individual variability in disease progression and severity at time of presentation. All outcome measures except mortality were continuous. Given the varied entry points and length of follow up for individuals in this retrospective cohort, time was treated as linear and specified as the number of days since the first measurement of each outcome variable, with first measurement as day 1. The effect estimate and p values were drawn from the interaction between the exposure variable and time in a model including main effects for exposure and time. Mortality analysis was conducted within a logistic regression model, using death at any point during the study period as the outcome. All outcomes were considered in independent models. Exposure variables were treated as continuous. Automobile-derived air pollution was measured by the log-transformed distance from subjects' residence to the nearest major road as the distribution was skewed and automobile-derived air pollution decays exponentially as distance increases.²⁷

After completion of initial analyses, potential confounders were added sequentially to the base model as covariates. Only variables that changed the point estimate of the β coefficient by greater than 15% were included in the final model.²⁸ Covariates assessed included study entry year, age, race, gender, baseline FVC, BMI, smoking status, the presence of comorbidities including COPD, GERD, pulmonary hypertension, and coronary artery disease, usage of medications including systemic corticosteroids, N-acetylcysteine, and immunomodulatory agents including azathioprine, mycophenolate, and methotrexate. The cohort predated the approval of pirfenidone and nintedanib. Age was continuous, and other variables were considered categorically. For longitudinal analyses, subjects were censored at time of death or lung transplantation. We estimated

that a sample size of 130 subjects would provide greater than 80% power to detect a 5% difference in FVC change between dichotomous category of exposure (split at the median), assuming mean FVC of 50% predicted and standard deviation of 10% in each group, at $\alpha=0.05$.

Results:

The initial EMR data query returned 238 subjects from Pennsylvania and New Jersey seen in our referral center between 2007 and 2013, 175 of which had sufficient longitudinal data for inclusion. 26 (15%) subjects missing exposure data were excluded from the study, and 14 (8%) subjects were determined to be misclassified as IPF based on manual chart review and adjudication, leaving 135 subjects in the final analysis. Characteristics of the study population are presented in Table 1. Excluded subjects had poorer baseline functional measures than included subjects, but there were no significant differences in exposures between the groups (supplementary Fig 1).

The median distance from subjects' residences to the nearest EPA monitoring station was 15.0 kilometers (interquartile range (IQR) 8.2-33.2) for PM₁₀ and 11.2 kilometers (IQR 8.2-33.2) for PM_{2.5}. The median PM₁₀ level during the study period was 18.5 $\mu\text{g}/\text{m}^3$ (IQR 16-24), and the median PM_{2.5} level was 10.5 $\mu\text{g}/\text{m}^3$ (IQR 9.5-12.5). PM₁₀ levels at all subjects' residences were below EPA National Ambient Air Quality Standards (NAAQS) throughout the study period while PM_{2.5} levels at some subjects' residences did not meet 2012 revised EPA NAAQS (although all levels were below 2006 NAAQS) (Figure 1). The median number of PFT measurements per subject was 5 (IQR 3-10).

There was a significant relationship between increased exposure to PM₁₀ and an accelerated FVC decline during the study period ($p=0.019$). Each 5 $\mu\text{g}/\text{m}^3$ increase in average ambient PM₁₀ concentration at subjects' residences corresponded with an additional 35 cc/year decline in FVC (95% CI 6-65cc/year) (Table 2). Figure 2 demonstrates this association graphically, comparing FVC decline in subjects with PM₁₀ exposure greater than the median over the study period to those with less than median exposure. This relationship persisted in a model accounting for a wide variety of

potential confounders. The main effect of PM10 on FVC was not significant ($p=0.569$). Of potential confounders, only baseline FVC changed the point estimate for the relationship between PM10 and the rate of FVC decline by more than 15% and was retained in the final model. In the final model, each $5\mu\text{g}/\text{m}^3$ increase in PM10 corresponded with an additional 46 cc/year decline in FVC (95% CI 12-81cc/year) (Table 3, Supplementary Table 2). In sensitivity analyses, this relationship did not significantly change when subjects whose PFTs were performed outside of our university health system or prior to 2007 were excluded (Supplementary Table 3).

There was no significant relationship between ambient PM2.5 and the rate of FVC decline, or between any of our exposure variables and the rate of decline in 6MWT distance (Table 2) or the odds of mortality during the study period (Table 4). There was a significant relationship between increased exposure to PM2.5 and an accelerated rate of increase in oxygen use on 6MWT (Table 2). Each $5\mu\text{g}/\text{m}^3$ increase in ambient PM2.5 concentration at subjects' residences corresponded with an additional 1.15 liters/year increase in oxygen use on 6MWT (95% CI 0.03-2.26L/year). There were no significant relationships between PM10 exposure and supplemental oxygen use, or between road proximity and any of our outcome measures (Supplementary Table 4).

Discussion:

Our study demonstrates a significant relationship between exposure to ambient particulate matter (PM10) and the rate of decline in FVC, a widely accepted indicator of disease progression in IPF. Higher PM10 exposure levels were associated with an accelerated rate of decline, even as all PM10 exposures met EPA NAAQS. The association between PM10 and FVC decline suggests that exposure to air pollution may be a contributing factor in a dysregulated response to alveolar epithelial injury leading to fibrosis.

It is intriguing that a significant relationship was seen between exposure to coarse (PM10) but not fine particulate matter (PM2.5) and the rate of decline in FVC, as there is an inverse relationship between particle size and penetration into distal airways, and a

higher concentration of fine particulates (PM_{2.5}) reach distal airways in experimental models of particulate exposure. It is likely that our findings were influenced by the greater variability in PM₁₀ exposure seen in the geographic catchment area of the study, perhaps due to the more fully aerosolized nature of PM_{2.5} (Figure 1). Nevertheless, in the context of recent studies demonstrating aberrant responses in bronchial epithelium in IPF, our findings may suggest a broader epithelial dysfunction in the pathogenesis of IPF than has previously been apparent.^{29,30} The significant relationship between PM_{2.5} exposure and increased use of supplemental oxygen in 6MWT over time lends strength to our primary finding, and suggests that the cumulative burden of exposure to ambient PM, rather than a size-specific effect of PM₁₀ exposure, leads to accelerated functional decline in IPF.

No association was seen between the proximity of subjects' residences to major roads and highways and any of our outcome measures. Previous studies of traffic-related air pollution have demonstrated an exponential decline in the concentration of ambient particles as the distance from major roadways increases. In part due to the size of the population included in the current study, there were very few subjects who lived within a short distance of a major road. This small sample size may have resulted in a failure to capture an association if one did exist.

This study included a wide geographic catchment area spanning urban and rural areas, which resulted in high variability in subjects' exposure to particulate pollution. The inclusion of subjects captured at varying time points in their disease progression decreases the possibility of systematic geographic bias in referral and lead time. Adjustment for calendar time and the use of potentially harmful medications reduces the risk of confounding by temporal trends in care delivery. The mixed-effect longitudinal model also makes relatively modest assumptions with respect to missing data. The diagnosis of IPF was made by clinicians with subspecialty expertise in the diagnosis and management of ILD, with multidisciplinary adjudication in cases of diagnostic uncertainty, leading to a precise IPF case definition. Nearly all PFTs were performed and

recorded by trained technicians at a central laboratory according to established criteria, leading to reliable and reproducible outcome measures.

This study has several important limitations. It is a single center study of patients from a single, albeit diverse geographic area, which limits the variability of exposure to PM, particularly PM_{2.5}. In addition, an approach to exposure relying on listed residence in the EMR and data from regional monitoring stations limits the precision with which true PM exposure can be ascertained. Furthermore, confounding by environmental or subject-specific factors not captured in the medical record or selection bias due to differential loss to follow up based on geographic factors unrelated to ambient air pollution may obscure the nature of the association.

Despite these limitations, this study demonstrated an association between exposure to ambient particulate matter and important clinical indicators of disease progression in IPF. The identification of a potentially modifiable contributing factor to progression of disease through environmental exposure to particulate air pollution may have implications for clinical management of the disease.

Table 1: Characteristics of the Study Population

Variable	
Age in years (median, range)	68 (46-92)
Gender (% male)	75%
Race	
White	74%
African American	8%
Other	17%
BMI (kg/m ²)	
< 25	27%
25-30	44%
30-35	20%
>=35	9%
Smoking status	
Current smoker	<1%
Former smoker	64%
Never smoker	36%
Pack-year history	
>= 40	15%
< 40	50%
0	35%
Comorbidities	
Chronic Obstructive Pulmonary Disease	8%
Gastroesophageal Reflux Disease	28%
Pulmonary Hypertension	11%
Medications	
Corticosteroids	50%
Steroid-sparing immunosuppressive agents	14%
NAC	32%
Deaths during study period	59 (44%)
Transplantations during study period	17 (13%)
Followup Time in Days (Median, IQR)	543 (244, 1128)
Number of Pulmonary Function Tests (Median, IQR)	5 (3, 9)
Baseline Pulmonary Function Testing (median, IQR)	
Forced Vital Capacity (Liters)	2.6 (2.0, 3.1)
Forced Expiratory Volume in 1 Second (L)	2.1 (1.7, 2.7)
Total Lung Capacity (ml/minute/mmHg)	4.0 (3.3, 4.8)
Diffusion Capacity of Carbon Monoxide	11.5 (8.9, 14.3)
Baseline Six minute walk distance (feet)	1228 (935, 1538)
Supplemental oxygen required to maintain saturation > 88% on Six Minute Walk Test (L)	0 (0, 4)

Table 2: Associations Between Average Particulate Matter Exposure and the Rate of Decline of Functional Measures of Disease Progression

	Exposure	Attributable change* (95% CI)	P value
Forced Vital Capacity (cc/year/5µg/m ³)	PM10	-35 (-65, -6)	0.019
	PM2.5	34 (-60, 127)	0.48
Six Minute Walk Distance (feet/year/5µg/m ³)	PM10	-1 (-18, 16)	0.90
	PM2.5	-15 (-70, 40)	0.59
Supplemental oxygen use required to maintain saturation > 88% on 6MWT (liters/year/5µg/m ³)	PM10	0.15 (-0.03, 0.1)	0.51
	PM2.5	1.15 (0.03-2.26)	0.044

* Units in this column are based on the Beta coefficient from the linear mixed effects model, converted into clinically meaningful units. For example, each 5µg/m³ unit increase in average PM10 exposure for each individual is associated with an additional 35cc decline in Forced Vital Capacity per year

Table 3: Change in the association between average PM10 concentration and the rate of FVC decline with adjustment for potential confounders.

Adjustment for potential confounders	Effect estimate for PM10-attributable change ¹	% change from unadjusted model ²	P value ³
None	-35	ref	0.019
Age	-36	1.0%	0.018
Gender	-36	1.0%	0.019
Race	-40	14.0%	0.008
Job-based SES	-38	7.3%	0.024
BMI	-35	0.0%	0.019
Comorbid COPD	-35	0.0%	0.019
Comorbid GERD	-35	0.5%	0.019
Comorbid pHTN	-35	0.0%	0.019
Use of steroids	-35	0.5%	0.018
Use of steroid sparing agents	-35	0.0%	0.019
Smoking status (never/former/current)	-35	0.0%	0.019
Pack-year history	-35	-0.5%	0.019
Year of study entry	-34	-2.6%	0.021
Baseline FVC ⁴	-46	30%	0.008

1: Units in this column are based on the Beta coefficient from the linear mixed effects model for the association between PM10 and rate of FVC decline in the model adjusting for the covariate of interest, converted into clinically meaningful units (cc/year/5 μ g/m³ increase in average PM10 exposure). For example, in a model adjusting for age, each 5 μ g/m³ unit increase in average PM10 exposure for each individual is associated with an additional 36cc decline in Forced Vital Capacity per year.

2: % change in the point estimate for the primary association between PM10 and the rate of decline in FVC in the model adjusting for the covariate of interest. No covariates changed the point estimate for this association > 15%.

3: P value for the primary association between PM10 and rate of decline in FVC in model adjusted for covariate of interest

4: Covariate included in final model

Table 4: Odds ratios for mortality in unadjusted analysis

	PM10 ²	PM2.5 ²	Road distance ³
Odds ratio for death ¹	0.95 (95% CI 0.69-1.29) p = 0.70	0.91 (95% CI 0.38-2.20) p = 0.85	1.00 (95% CI 0.97-1.03) p = 0.79

1: Odds ratio for documented death at any time during the study period for each unit increase in the variable of interest

2: PM concentration in these columns are converted to clinically meaningful units (5µg/m³). Odds ratio represents the odds of documented death during the study period for each 5µg/m³ increase in average PM concentration.

3: Road distance in this column is converted to clinically meaningful units (100 meters). Odds ratio represents the odds of documented death during the study period for each 100 meter increase in distance from nearest major road.

Figure 1: Distribution of average Particulate Matter exposure during the study period for all subjects included in longitudinal analysis

Median, IQR and maximum/minimum value for the average annual concentration of PM10 and PM2.5 for each individual during the study period.

Figure 2: Average Forced Vital Capacity trajectory over time, compared between subjects with PM10 concentrations greater than or less than the median exposure level

Pooled trajectory of average FVC (mean, 95% CI) over time from study entry point, split dichotomously between individuals with PM10 exposure above and below the median level of exposure. The steeper trajectory in those with above-median exposure reflects the relationship between PM10 exposure and FVC decline, although the pooled analysis does not capture the statistical power of the mixed-effects model.

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CJW and JDC are the guarantors of the study and take responsibility for the integrity of the data and the accuracy of the data analysis. CJW and JDC drafted the manuscript. CJW performed the data analysis under the supervision of JDC and ARL. CJW, JDC, RJS, KCP, MEK, TMP, RAP, KH, and TJ contributed to study design. CJW, RJS, KCP, MEK, LAL and WTM contributed to case adjudication. CJW, KH, TJ, and BRL contributed to data collection. All authors contributed to the interpretation of the data, critical revision of the final manuscript, and approve the final version of the manuscript.

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JDC has received institutional grant funding from Bristol Myers Squibb for the study of IPF. MEK has received research support as a site PI for clinical trials for the treatment of IPF from MedImmune, Sanofi, Genetech and Gilead Sciences. BRL has received research support as site PI for clinical trial for pulmonary hypertension from Actelion, and serves on an advisory board for Gilead Sciences.

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